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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,084	VAUTHIER ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-20* is/are pending in the application.

4a) Of the above claim(s) *7,11-14,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,8-10,15,16,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant had elected with traverse the invention of Group I, Claims 1-10, drawn to a compound comprising a hemoprotein associated with a sequenced block copolymer comprising a hydrophilic segment that is an oligosaccharide or a polysaccharide linked to at least one hydrophobic segment of Formula I and a method of using said compound as a human or animal blood substitute.

Within Group I, Applicant has elected:

i) the "X" moiety species to be CN, as recited in Claims 1 and 4;

ii) the "Y" moiety species to be of the formula "COOR-prime", as recited in Claim 1.

iii) the hemoprotein species "i", wherein the hemoprotein is a "normal hemoprotein" as recited in Claim 2, and

iv) the hydrophilic segment species "ix", wherein the hydrophilic segment is heparin, as recited in Claim 6.

Amendments

In the reply filed September 8, 2009, Applicant has cancelled Claims 3-4 and 21-23, withdrawn Claims 7, 11-14 and17-18, amended Claim 1.

Claims 7, 11-14 and 17-18 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

This application contains claims drawn to an invention nonelected with traverse in the reply filed on November 29, 2006. In the Office Action mailed December 15, 2006, the Examiner indicated that the restriction/election was made FINAL. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-2, 5-6, 8-10, 15-16 and 19-20 are under consideration.

Priority

Acknowledgement is made of the certified translation, filed on April 17, 2007, of the French patent FR 02/11518 filed on September 17, 2002.

Accordingly, the effective priority date of the instant application is granted as September 17, 2002.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the September 8, 2009 response will be addressed to the extent that they apply to current rejection(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

1. **The prior objection to the amendment filed December 23, 2008 is withdrawn** in light of Applicant's amendment to the specification, papers filed September 8, 2009, to cancel the new matter.

Claim Objections

2. **The prior objection to the claims is withdrawn** in light of Applicant's amendments to the claims.

Claim Rejections - 35 USC § 112

3. **The prior rejection of Claims 21-23 under 35 U.S.C. 112 first paragraph, is withdrawn** in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 103

4. **The prior rejection of Claims 1-2, 5-6, 8-10, 15-16 and 19-23 under 35 U.S.C. 103(a)** as being obvious over Chauvierre et al (WO 02/39979 A1; *of record, U.S. equivalent is 2004/0028635) and Schmidt et al (U.S. Patent 4,698,387) and Desai et al (U. S. Patent No. 6,096,331; *of record) **is withdrawn** in light of Applicant's amendment to the claims to recite "consisting essentially of". The instant specification discloses that the saccharide may or may not be modified, as defined in WO 02/39979 (pg 4, lines 5-8) which discloses that the modification occurs on the polysaccharide backbone, i.e. the grafting of chemical entities. Schmidt does not teach the modification of the polysaccharide backbone, and thus does not teach a modified polysaccharide per the instant definition embraced by "consisting essentially of".

5. **Claims 1-2, 5-6, 8-10, 15-16 and 19-20 are rejected under 35 U.S.C. 103(a)** as being obvious over Chauvierre et al (WO 02/39979 A1; *of record, U.S. equivalent is 2004/0028635) in view of Kabanov et al (U.S. Patent 6,333,051), Schmidt et al (U.S. Patent 4,698,387; *of record), and Desai et al (U. S. Patent No. 6,096,331; *of record).

Determining the scope and contents of the prior art.

Chauvierre et al disclose the synthesis of nanoparticles of 1nm to 1mm [0045-46] consisting essentially of a core portion and a surface portion forming a sequenced block copolymer, said core portion consisting essentially of at least one hydrophobic segment having the formula as taught in Formula I, wherein "X" may be a "CN" moiety, wherein the hydrophobic segment may be a poly(alkylcyanoacrylate) [0010-0019], [0039] [0043-44] conjugated to a saccharide hydrophilic that may be heparin [0028]. Chauvierre et al teach that the inventive delivery system(s) may be used to administer a therapeutic agent, i.e. proteins, to an animal or patient [0049-50].

Chauvierre et al do not disclose the biological agent is non-covalently associated with the nanoparticle comprising the block copolymer and hydrophilic segment that may be heparin. However, at the time of the invention, Kabanov et al disclosed nanoparticles comprising block copolymer networks (col. 3, lines 9-11; col. 4-col. 5, line 7) comprising polysaccharides such as heparin (col. 30, line 27), wherein the polymer networks can trap molecules non-covalently during the particle synthesis (col. 8, lines 63-67; Examples 7-9). The polymer network can also be loaded non-covalently with the biological agent after the network is synthesized (col. 13, lines 1-22; Examples 7-9), wherein the polymer network captures the biological agent that may be a protein (col. 20, lines 33-35).

Neither Chauvierre et al nor Kabanov et al disclose the use of a heparin-coated nanoparticle for the delivery of hemoproteins, more specifically hemoglobin. However, at the time of the invention, Schmidt et al disclosed a composition comprising a conjugate between hemoglobin and an adduct comprising an anionic ligand and a macromolecular agent, wherein the macromolecular agent may be a polysaccharide (col. 4, lines 6-13). The macromolecular agent is chemically linked with an adduct ligand, thereby binding hemoglobin by way of a non-covalent bond (col. 4, lines 39-45). The hemoglobin conjugates can be used as hemoglobin-containing blood substitutes, and are able to reversibly bind and release molecular oxygen (col. 5, lines 25-27). The intended use of the product is a blood substitute suitable as an oxygen and carbon dioxide carrier (col. 3, lines 18-20), and thus said product is "gas-associated".

Neither Chauvierre et al, Kabanov et al nor Schmidt et al disclose the blood substitute product to comprise saline. However, at the time of the invention, Desai et al taught the synthesis of nanoparticles comprising synthetic block copolymers (col. 10, lines 3-22), attached to biocompatible materials, i.e. polysaccharides (col. 9, lines 42-49) to form a polymeric shell. Desai et al also contemplate that hemoglobin would be associated with the polymeric shell (col. 9, line 54; col. 11, line 63), thereby providing a blood substitute. Given that Desai et al contemplate the use of a hemoglobin-containing nanoparticle for use as a blood substitute, one of ordinary skill in the art would reasonably expect said composition to be "gas-associated". Desai et al disclose the nanoparticle product may diluted in saline for delivery (col. 6, line 29; col. 11, lines 10-13; Example 6, col. 17, line 15; Example 12, col. 21, lines 3-4).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in synthesizing nanoparticles and artificial blood substitutes for therapeutic purposes. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to modify the heparin-coated poly(cyanoacrylate) nanoparticle of Chauvierre et al to comprise hemoglobin conjugated non-covalently as taught by Kabanov et al and Schmidt et al for the formation of a blood substitute product with a reasonable expectation of success because Kabanov et al successfully demonstrated the ability to non-covalently associate a biological agent, e.g. a therapeutic protein, to a nanoparticle comprising a nanogel network, wherein said nanogel network may comprise heparin, Schmidt et al successfully demonstrated the manufacture of polysaccharide-hemoglobin conjugates for the formation of a blood substitute in which the hemoglobin is attached non-covalently to the polysaccharide, and Applicant's own work teaches that prior to the instantly asserted invention, those of ordinary skill in the art had long recognized that heparin, being polyanionic in nature, has a high affinity for basic proteins like hemoglobin (Haney et al, 2000; reference 19 of Chauvierre et al, 2004a; * of record), and thus those of ordinary skill in the art would immediately recognize a reasonable expectation of success for the formation of a non-covalent association between hemoglobin and heparin. An artisan would have been motivated to modify the heparin-coated poly(cyanoacrylate) nanoparticle of Chauvierre et al to comprise

hemoglobin conjugated non-covalently as per Kabanov et al and Schmidt et al for the formation of a blood substitute product because the heparin moiety, well known in the art to act as an anti-coagulant as well as to inhibit complement activation, already tailors the nanoparticle for increased circulating half-life of the nanoparticle, and thus would provide an artisan with the desired delivery vehicle for a blood substitute, and Schmidt et al disclose that all of the hemoglobin-containing molecules comprising a covalent bond between the cross-linking agent or polymer results in a change in the hemoglobin structure, thereby adversely affecting oxygen transport, impairing oxygen release, reduced hemoglobin cooperativity, and an undesired increase in oxygen affinity disadvantageous for use as a blood substitute (col. 2, lines 16-53). The non-covalent association of hemoglobin with the polysaccharide-ligand overcomes the art-recognized disadvantageous properties.

It also would have been obvious to one of ordinary skill in the art to substitute a carrier/buffer as taught by Chauvierre et al and/or Kabanov et al and/or Schmidt et al with saline as taught by Desai et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, those of ordinary skill in the art have long-recognized saline to be a pharmaceutically acceptable carrier/buffer for the delivery of pharmaceutical compositions, and saline (Desai et al) would perform the same art-recognized functions as the carriers/buffers of Chauvierre et al and/or Kabanov et al and/or Schmidt et al.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Response to Arguments

Pages 9-18 of Applicant's Arguments/Remarks Made in Amendment provides arguments that are duplicated from the Applicant's Arguments/Remarks Made in Amendment filed December 23, 2008. Such were considered in the prior Office Action, and will not be iterated

herein. The Examiner will address Applicant's new argument(s) pertaining to the instant rejection.

Applicant argues that Schmidt fails to teach or suggest a particle structure of the claims wherein hemoglobin, for example, is non-covalently associated to a surface of a particle wherein the surface of the particle consists essentially of a polysaccharide or oligosaccharide. Any particle formed by Schmidt or suggested by Schmidt would presumably not have a surface portion required by the structure of the presently claimed invention.

Applicant's argument(s) has been fully considered, but is not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Kabanov et al successfully demonstrate the ability to non-covalently associate a biological agent, i.e. a therapeutic protein, to a nanoparticle consisting essentially of a block copolymer and a hydrophilic segment, wherein said hydrophilic segment may comprise heparin. Applicant's own work teaches that prior to the instantly asserted invention, those of ordinary skill in the art had long recognized that heparin, being polyanionic in nature, has a high affinity for basic proteins like hemoglobin (Haney et al, 2000; reference 19 of Chauvierre et al, 2004a; * of record), and thus those of ordinary skill in the art would immediately recognize a reasonable expectation of success for the formation of a non-covalent association between hemoglobin and heparin.

Conclusion

6. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633